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Fragile-X Carrier Females: Evidence for a Distinct Psychopathological Phenotype?

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The present study examined 35 mothers (29 premutation carriers) of children with fragile-X syndrome in measures of intelligence and psychiatric disorders by comparing them with two control groups: a) 30 mothers of children in the general population and b) 17 mothers of non-fra-X retarded children with autism.

Premutation carriers had a higher frequency of affective disorders than mothers from the general population. Preliminary data indicate that normally intelligent premutation carriers of the fra-X genetic abnormality have a similar frequency of affective disorders (DSM-III-R criteria [APA, 1987]) than mothers of autistic children. Neither carriers of the premutation nor carriers of the full mutation in the fra-X group obtained a diagnosis of the schizophrenia-spectrum (schizophrenia, schizophreniform disorder, and schizoaffective disorder). Carriers of the fra-X full mutation had considerably lower IQ than carriers of the fra-X premutation. There was a negative correlation between length of CGG repeats and IQ which failed to reach significance in both groups of fra-X carriers. Psychiatric morbidity was not restricted to carriers of the fra-X full mutation only but was also present in normal intelligent premutation carriers.

Furthermore the age of onset of psychiatric morbidity in both groups of mothers of fra-X children as well as the group of mothers with autistic children was much earlier than the age when mental retardation had been diagnosed in their children. Increased psychosocial burden of raising a developmentally retarded child and/or feelings of guilt of being a fra-X carrier can therefore not fully explain our findings (three-fold higher frequencies of affective disorders compared to mothers from the general population).

KEY WORDS: fragile-X syndrome, affective disorders, schizophrenia, autism

INTRODUCTION

Apart from its genetic aspects, the fragile-X syndrome (fra-X) has attracted the interest of researchers because of its putative relationship to major psychiatric conditions. Whereas some of the early optimism regarding a high prevalence of autism in fra-X males with the full syndrome has been refuted (for critical review see Fisch [1993]), the relationship between female obligate carriers of fra-X and psychiatric disabilities is still obscure. Debate regarding excess of psychiatric disorders in fra-X females currently surrounds questions such as whether the increased psychosocial burden of raising a developmentally retarded child explains feelings of guilt, social avoidance, or depressive mood, whether the primary effect of the mutation affecting the FMR-1 gene (mental retardation or below-average IQ) leads to a secondary effect on psychiatric morbidity, or whether psychiatric disorders represent a direct, primary consequence of the fra-X pre- or full mutation.

Excess rates of depressive disorders in female obligate carriers of fra-X have been found consistently in several studies [Reiss et al., 1988; Freund et al., 1992; Thompson et al., 1994]. Higher frequencies of mood disorders (>40%), psychopathological traits such as schizotypy and lower premorbid adjustment level were observed within the group of fra-X carrier females with X fragility compared to cytogenetic negative fra-X females [Freund et al., 1992], as well as in those females with maternal inheritance compared to females

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with paternal inheritance of their fragile site [Reiss et al., 1989]. A recent study indicated that both pre- and full mutation carriers have schizotypal traits, albeit in lower frequency than previously reported [Sobesky et al., 1994].

The literature regarding psychiatric morbidity in fra-X females is increasing, but most studies reveal shortcomings. Early anecdotal reports about "shyness" and "psychotic problems" [Fryns, 1986] are of limited scientific value. More recent studies using structured clinical interviews for the assessment of psychiatric diagnoses neglected an exact determination of the intelligence level of their subjects (by using approximation measures of IQ only). Since prevalence rates of psychiatric dysfunction in mentally retarded individuals are between 12 and 30% [Fisch, 1993] and a considerable proportion of fra-X carrier females has below-average IQ levels (in the study of Cronister et al. [1991] up to 50%!) psychiatric research within the group of obligate female fra-X carriers should be conducted by meticulous assessment of IQ in order to address the impact of IQ on psychiatric morbidity within this group.

Furthermore, the CGG-amplification status of fra-X carrier females seems to affect IQ: premutation carriers are reported to have a significantly higher IQ than females with the full mutation [Thompson et al., 1994]. Studies including this molecular technique in relationship to psychiatric assessment are still rare and demonstrated divergent results. Whereas premutation carriers sometimes did not differ from controls in the frequency of psychiatric disabilities [Reiss et al., 1993], Hull and Hagerman [1993] were able to show that the phenotype (including some behavior traits) of premutation carriers differs from the one of controls and resembles the one of full mutation carriers. Finally, Thompson et al. [1994] reported higher frequencies of major depression in carriers of the premutation (75%) compared to carriers of the full mutation (60%), although this difference was not statistically significant and sample size was small.

The putative interaction of psychiatric disabilities with IQ of fra-X carrier females might be mediated by the difference in CGG-amplification status of the patients. Consequently, psychiatric research within groups of fra-X carrier females should also focus on the measure of CGG-amplification in order to provide more information about the function of the mutant gene.

Based on previous reports in the literature, the present investigation, therefore, addresses the following hypotheses by using structured interviews for the assessment of psychiatric diagnoses [Nurnberger et al., 1994] as well as reliable and valid diagnostic criteria [DSM-III-R [APA, 1987]] and standardized IQ measurement (WAIS-R): 1) Female carriers of the fra-X pre- or full mutation (unrelated mothers of children with fra-X mental retardation) have a higher frequency of psychiatric disorders (e.g., affective disorders) than a control group of unrelated mothers of non-fra-X autistic children and a control group of unrelated mothers of children recruited in the general population. 2) The psychosocial burden of raising a developmentally retarded child explains the excess of psychiatric disorders in the group of mothers with fra-X children and in the group of mothers with non-fra-X autistic children compared to mothers of normal developing children. 3) Psychiatric morbidity in female fra-X carriers is restricted to individuals carrying the full mutation and/or individuals with below-average IQ. 4) CGG-amplification status (pre- or full mutation) has an impact on IQ and secondarily leads to higher frequencies of psychiatric disorders.

METHODS

Sample

Thirty-five unrelated biological mothers of children with fra-X syndrome were recruited from the national support group of fragile-X syndrome in Germany ("Interessengemeinschaft Marker X e.V."). The diagnosis of fra-X in children and the fra-X carrier status of their mothers was made independently from this study by regional Institutes of Human Genetics in Germany. However, investigators of this study were blind to their exact molecular status (pre- or full mutation, size of CGG repeat).

The study comprises two control groups: a) 17 unrelated mothers of non-fra-X retarded children with autism and b) 30 unrelated mothers of normal developing children from the general population. We tried to keep interviewers blind to diagnosis, but since mothers of fra-X as well as mothers of autistic children already knew the diagnosis of their children we could not meet this intention in all cases.

All groups were matched according to sociodemographic variables (Table I) to a fairly high degree. Mothers of autistic children tended to be older than the other mothers. However, mothers of autistic children did not differ from mothers of fra-X children with respect to their age when the diagnosis of autism or fra-X was made in their children.

Mothers of fra-X children and mothers of autistic children were further matched according to degree of adaptive behavior level of their children by an abbreviated version of the Vineland scale. The control group of mothers from the general population was drawn from a large cohort of representative individuals recruited as controls for research purposes for a family study of psychiatric disorders [Maier et al., 1993]. Subjects were informed about the scientific purpose of this evaluation.

Psychopathological Assessment

All subjects in this study were interviewed by an experienced psychiatrist (P.F. or O.W.) with the DIGS Interview addressing major psychiatric disorders (for exact description, see Nurnberger et al. [1994]). Best estimate diagnoses were made by taking into account all available information about the particular individual: personal interview and diagnosis obtained with the DIGS, information from significant others (husband or relatives), medical records (if available), and behavior during the interview [Leckman et al., 1982]. Final diagnoses of each subject was made by a consultant psychiatrist (W.M.) according to DSM-III-R criteria [APA, 1987].

TABLE I. Sociodemographic Variables of All Groups

Lifetime diagnoses (DSM-III-R)	Mothers of fra-X children		Mothers of autistic children	Control mothers (general population)
	Premutation carriers	Full mutation carriers		
n	29	6	17	30
Age	38.7 (± 7.5)	40.8 (± 8.5)	48.6 (± 9.4)	39.3 (± 9.9)
Age at diagnosis (fra-X or autism of their children)	33.7 (± 4.6)	36.6 (± 7.4)	36.6 (± 8.2)	—
Age of onset of main *psychiatric diagnosis*	25.2 (± 8.7)	20.0 (± 4.4)	29.2 (± 10.8)	34.7 (± 7.6)
Number of children	2.1	2.5	2.1	1.9
Number of affected children	1.2	1.8	1.1	—
Full scale IQ	110.2 (± 16.6)	86.5 (± 14.4)	107.2 (± 19.4)	116.1 (± 13.3)

Each mother in the four comparison groups was asked for major psychiatric disorders in their family (first, second, and third degree relatives) by screening questions for psychotic disorders, affective disorders, substance abuse, and suicidal behavior. Whenever screening questions of one of these domains were answered with "yes," the interviewer went on asking further questions according DSM-III-R criteria [APA, 1987] for that particular diagnosis.

Intelligence Assessment

Each individual in the four comparison groups was administered the WAIS-R, a standardized instrument for IQ assessment, providing individual scores for verbal, performance, and full scale IQ. Intelligence assessment was made by psychologists and supervised by an expert psychologist (M.H.).

Statistics

In a first step, frequencies of DSM-III-R diagnoses in the four different groups of mothers were compared with an overall Chi^2-test (2 × 4 table). Additionally, if the result of the overall test was significant, hierarchically sub-ordered four-fold-tests (Fisher's exact test) were computed to analyze the *P*-values for single-group comparisons between two groups.

Molecular Assessment

Blood samples were obtained from all women of the fra-X support group for exact determination of fra-X carrier status (pre- or full mutation and exact size of CGG-repeat). Analysis was made by U.F. and S.G.S.

Mothers of non-fra-X autistic children were recruited from the Department of Child & Adolescent Psychiatry in the University of Frankfurt and were all members of a support group for autistic individuals. Fra-X carrier status had been excluded in all of them, analysis was made in an independent Institute of Human Genetics.

RESULTS

Frequency of Psychiatric Disorders in the Four Comparison Groups

Table II represents the primary lifetime diagnoses in each group of subjects. Secondary diagnoses (e.g., secondary alcohol abuse or anxiety disorder) are not mentioned in Table II. Additionally, only the overall diagnostic categories are listed.

None of the women in the two fra-X carrier groups and the mothers of the control group from the general population obtained any diagnosis from the schizophrenia spectrum. One mother of an autistic child received a diagnosis of psychotic disorder NOS.

TABLE II. Psychiatric Lifetime Diagnoses in All Groups

Lifetime diagnoses (DSM-III-R)	Mothers of fra-X children		Mothers of autistic children	Control mothers (general population)
	Premutation carriers	Full mutation carriers		
n	29	6	17	30
Any psychotic disorder[a]	0	0	1 (5.9%)	0
Any affective disorder[b]	13 (44.8%)	2	10 (58.8%)	4 (13.3%)
Any anxiety disorder[c]	5 (17.3%)	0	1 (5.9%)	1 (3.3%)
Other diagnoses[d]	3 (10.3%)	0	1 (5.9%)	1 (3.3%)
No diagnoses	8 (27.6%)	4	4 (23.5%)	26 (80.0%)

[a]Includes schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS.
[b]Includes unipolar major depression, bipolar affective disorder (I and II), dysthymia, affective disorder NOS.
[c]Includes panic disorder with or without agoraphobia, social phobia, generalized anxiety disorder.
[d]Includes alcohol abuse, somatoform disorder, eating disorder NOS.

Carriers of the fra-X premutation had a higher frequency of affective disorders than the group of mothers in the general population ($P = 0.018$). However, the difference between full mutation carriers and controls failed to be significant ($P > 0.05$) because of limited sample size of full mutation carriers. Although there was a trend for mothers of autistic children for higher frequencies of affective disorders than pre- and full mutation fra-X carriers, this trend was not statistically significant ($P > 0.05$). Mothers of autistic children received significantly more frequently a diagnosis from the affective spectrum ($P = 0.004$) than control women from the general population.

There also was a three-fold higher frequency of anxiety disorders in the group of mothers of fra-X children compared to mothers of autistic children and mothers from the general population.

Mean age of onset for any psychiatric disorders within the group of unrelated mothers with fra-X children carrying the premutation was 25.2 (± 8.7) years and age of onset for full mutation carriers was 20.0 (± 4.4) years. Furthermore, their mean age was 33.7 (± 4.6) years for premutation carriers and 36.6 (± 7.4) years for full mutation carriers when their child received the specific diagnosis of fra-X mental retardation. Mean age of onset for psychiatric diagnoses of mothers of autistic children was 29.2 (± 10.8) years whereas their mean age was 36.6 (± 8.2) years when they had been told that their children had autism (see Table I).

Family History Information-Based Psychiatric Disorders

Thirty-five unrelated mothers with fra-X children had been asked about major psychiatric disorders within their families. Since sample size of full mutation carriers was too low, pre- and full mutation carriers were pooled. A frequency of 17.1% of psychotic disorders (schizophrenia, schizoaffective disorder, and psychotic disorder NOS) was reported in relatives of these female fra-X carriers. None of the mothers of autistic children or mothers from the general population reported any relative having psychotic disorders.

Relatives of female fra-X carriers had a frequency of affective disorders of 20%, compared to only 11.7% of the relatives of mothers of autistic children and 3.3% of the relatives of mothers from the general population. Interestingly, approximately similar frequencies of alcohol dependence were found in relatives of fra-X carrier mothers (17.1%) and mothers of autistic children (17.7%). Furthermore, suicide occurred with similar frequency in families of mothers with fra-X children (11.4%) than in families of mothers with autistic children (11.7 %).

IQ Distribution in the Four Comparison Groups

The highest IQ was found in the group of mothers in the general population, which followed a normal distribution (mean: 116.4 ± 13.3); premutation carrier mothers of fra-X children obtained a lower full scale IQ score mean of 110.2 ± 16.6 and mothers of autistic children scored a mean of 107.2 ± 19.4. The lowest full scale IQ scores were measured in the group of mothers carrying the fra-X full mutation: 86.5 ± 14.4 (ANOVA; $F = 7.06$; $P < 0.001$).

In contrast to approximately similar scores of verbal and performance IQ in mothers from the general population (verbal IQ: 115.8 ± 10.4; performance IQ: 117.9 ± 13.2) and premutation carriers (verbal IQ: 108.6 ± 14.4; performance IQ 107.1 ± 16.3), full mutation carriers tended to have higher verbal than performance IQ scores (verbal IQ: 91.2 ± 16.2; performance IQ: 85.7 ± 12.8) and mothers of autistic children revealed just the opposite pattern (verbal IQ: 103.5 ± 16.4; performance IQ: 108.0 ± 18.8).

Relationship Between IQ and Length of CGG Repeat in fra-X Carrier Females

Within the group of female fra-X carriers we found a significant negative correlation between size of CGG repeat and full-scale IQ ($r = -0.47$; $P = 0.038$) and verbal IQ ($r = -0.49$; $P = 0.032$), whereas performance IQ just failed to reach significance ($r = -0.037$; $P = 0.085$). When this analysis was performed separately for premutation and full mutation carriers, the negative correlation remained but failed to reach significance, probably due to low sample size.

There was a trend for those fra-X carriers without any psychiatric diagnosis to have a lower IQ and a larger size of CGG repeats in comparison to those carrier females with affective disorders who tended to have a higher IQ and a smaller size of CGG repeats.

DISCUSSION

This is the first investigation of female fra-X carriers and control groups using the maximal current standard of methods in psychiatric epidemiology (particularly best estimate diagnoses [Leckman et al., 1982]) applied by experienced clinical psychiatrists. The study included 1) a comprehensive semistructured clinical interview of psychiatric disorders, which was specifically designed for genetic studies (DIGS [Nurnberger et al., 1994]); 2) family history information about relatives of fra-X carrier females; and 3) exact assessment of intelligence level by the WAIS-R (Wechsler Adult Intelligence Scale-revised), which is the best validated intelligence test.

Our study confirmed earlier reports about psychiatric disabilities of fra-X carrier females. In pre- and full mutation carriers, affective disorders represented the most frequently observed diagnoses. It is important to note that affective disorders occurred in approximately 40% of premutation carriers, which was substantially higher than the frequency in women from the general population. Due to the small sample size of full mutation carriers (n=6), differences between pre- and full mutation carriers regarding frequency of affective disorders lacked statistical significance. When the fra-X pre- and full mutation carriers were pooled and compared to the control group of mothers of non-fra-X autistic children similar frequencies of affective disorders were observed in both comparison groups. In this respect our study closely matches previous studies [Reiss et al., 1988, 1989, 1993], which also demon-

strated no difference between fra-X individuals and controls (mothers of developmentally retarded children of unknown cause) regarding psychiatric disorders. However, none of these previous studies provided any information concerning family history of psychiatric disorders in their samples. Based on family history information, our group of fra-X carrier women had a high loading of psychiatric disorders and diagnostic subclassification of the family history pattern pointing to an aggregation of psychosis in the fra-X group. Psychosis *may either* represent variants of affective disorders or non-affective disorders. By family history method it is difficult to delineate between these possibilities. Furthermore, a subgroup of non-affective psychotic disorders may reflect a family genetic variant of affective disorders [Maier et al., 1993]. Thus, the elevated risk of psychosis in relatives of mothers carrying the fra-X mutation may represent the increased risk for major affective disorders among fra-X individuals in general. Therefore, further research is necessary in this area to determine whether those relatives reported to have psychotic disorders by family history method also are carriers of the fra-X mutation.

Psychiatric disabilities have been described before in fra-X carriers (as early as in 1943 in the original Martin-Bell pedigree [Martin and Bell, 1943]) but their relationship was said to be obscured by mental retardation since psychotic traits and mood disorders are not an unusual finding in mentally retarded persons [Fisch, 1993]. However, just the opposite is the case in our patients: a substantial portion of female premutation fra-X carriers in the present investigation manifested psychiatric morbidity but our patients definitely were *not* mentally retarded. Moreover, there was a trend for individuals presenting with any diagnosis from the affective spectrum to have a higher IQ and a smaller CGG repeat size in comparison to those female fra-X carriers without any psychiatric diagnosis. Therefore, we conclude that the excess rate of affective disorders in female fra-X carriers does not represent an epiphenomenon of mental retardation. In contrast, our data indicate that those fra-X carrier females who did not report psychological problems and consequently did not obtain any psychiatric diagnosis had a lower IQ. In this context it might be of interest that some investigators have speculated that a subgroup of fra-X carrier females might be less introspective, putatively less aware of emotional problems or simply deny them [Steyaert et al., 1994].

It may also be objected that recruitment of our female fra-X carriers from a support group leads to a potential bias, since people who seek help in a support group may have a different way of coping for the fact of being a fra-X carrier and to have a fra-X child (e.g., more extraverted behavior); however, this is very unlikely since we have chosen mothers of autistic children who are also members of a support group as controls.

Also, psychological stress has often been cited to explain the high rate of psychopathology in fra-X premutation carriers [Reiss et al., 1993]. Therefore, feelings of guilt, depressive mood or social avoidance may well be interpreted as a reaction to some unusual stress when raising a developmentally retarded child. In our control group of mothers with autistic children the rate of affective disorders was approximately similar to the fra-X premutation carrier group and three times higher than in women from the general population. Consequently, one may conclude that affective disorders reflect the emotional stress of having a mentally retarded child. However, age-of-onset analysis indicates that psychiatric disorders of fra-X carrier women and mothers of autistic children occurred on the average considerably earlier (in some individuals even in adolescence) than the mental retardation diagnosis of their children. Therefore, we assume that the "psychological stress hypothesis" may not account for all female fra-X carriers or mothers of autistic children.

Anxiety disorders were three times more common in our fra-X premutation carrier group compared to both of our control groups. The most striking difference was found with respect to social phobia which was prevalent in approximately 10% of the fra-X premutation carriers but in none of our control women. The mothers of autistic children in our study did not fulfill criteria for social phobia in contrast to a recent investigation by Smalley et al. [1995] who found a frequency of 20.2% among first-degree relatives of autistic patients. However, their sample comprised more than 40% male relatives (fathers and brothers), whereas our study included only mothers of autistic subjects. Thus, discrepancies between both studies may partly be due to gender effects.

CONCLUSION

It is evident from our data that female carriers of the fra-X premutation have a broad variety of psychopathological symptoms and the question emerges whether these individuals would benefit from psychopharmacological treatment. A preliminary report on this issue obtained positive results and significant improvement regarding depressive symptomatology, outburst behavior, as well as mood lability in male and female fra-X carriers [Hagerman et al., 1994]. Finally, it should be underlined that this study is in progress and the data are preliminary. Therefore, the results obtained up to now may only reflect a trend rather than definite facts. Further analysis is warranted concerning subgroups of affective disorders (e.g., frequency of unipolar and bipolar affective disorders) in fragile X carriers, the mode of parental inheritance, and its impact on psychiatric disorders in the group of pre- and full mutation fra-X carriers. Additionally, relatives of fra-X carriers should be assessed regarding genotype-phenotype interaction. We hope to be able to reaffirm and extend these preliminary results.

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